Genomic analysis reveals why asthma inhalers fail minority children

March 15 2018, by Nicholas Weiler

Esteban Burchard, MD, MPH, a physician-scientist in the Schools of Pharmacy and Medicine at UCSF

The largest-ever whole-genome sequencing study of drug response in minority children has revealed new clues about why the front-line

asthma drug albuterol does not work as well for African-American and Puerto Rican children as it does for European American or Mexican children.

Asthma is the most common chronic childhood disease in the world, according to World Health Organization estimates. Children with asthma experience difficulty breathing as a result of chronic inflammation of the airways, which can be alleviated by inhaling drugs called bronchodilators that make the muscles lining the airways relax, allowing them to reopen. Albuterol is the most commonly prescribed bronchodilator in the world, and often the only medication available to children in lower income settings.

However, albuterol and other inhaler drugs do not work equally well for all children. In the U.S., Puerto Rican and African-American children – who also have the highest prevalence of asthma nationwide – respond least well to these life-saving drugs. This may contribute to the four- to fivefold higher rate of death from asthma among these groups, compared to European Americans and Mexicans.

Researchers in the UCSF Asthma Collaboratory, directed by Esteban Burchard, MD, MPH, a physician-scientist in the Schools of Pharmacy and Medicine at UCSF, have been studying the genetics of asthma in minority populations for two decades. Previous genome-wide association studies (GWAS) by the group have identified new genetic risk factors for the higher rates of asthma and poor response to bronchodilator medications seen in these minority populations – in many cases different from risk factors seen in prior studies conducted in European Americans.

"Despite the much higher impact of asthma among African-American and Puerto Rican populations, over 95 percent of studies of lung disease have been performed on people of European descent," said Angel Mak,

Ph.D., the UCSF Asthma Collaboratory's director of genetic research. Mak was one of the lead authors on the team's newest study, published in an early online version on March 6, 2018 in the *American Journal of Respiratory and Critical Care Medicine*, the world's leading pulmonology journal.

In the new study, the lab has conducted the first large-scale whole genome sequencing study of asthma drug response in African Americans and Latino children in an effort to pin down the genetic factors contributing to reduced albuterol response more precisely than possible in previous association studies. The researchers examined the genomes of a diverse group of 1,441 children with asthma who had either very high or very low response to the drug. The genome sequencing was provided courtesy of Trans-Omics for Precision Medicine (TOPMed) Program of the National, Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health.

The researchers discovered new genetic variants associated with reduced albuterol response, implicating genes involved in lung capacity, immune response, and response to blockers and related medications in albuterol's weakened effect on these patients. One of the clearest associations was with a variant in the NFKB1 gene that is more prevalent in people with African ancestry. Closer examination of this gene variant suggested it may regulate the expression of a neighboring gene, SLC39A8, which is known to help protect the airways and lungs from inflammation and cellular damage.

These results reveal new risk markers in the genome that could be used to predict which children are likely to respond poorly to albuterol and other current first-line anti-asthma drugs, and to guide the development of new therapies that will be more effective and reduce the outsize burden of mortality in minority populations.

"These initial results from the NHLBI TOPMed program demonstrate the existing genetic basis underlying the racial and ethnic disparities in asthma," said James Kiley, Ph.D., director of the NHLBI Division of Lung Diseases. "This will be a tremendously invaluable resource supporting discovery research in asthma for years to come."

The researchers hope that more studies of minority children and asthma will follow – as it stands, there are too few other studies of nonwhite children to make it possible to replicate the study's findings in an independent group of patients, despite the collaboration of eight universities and 13 individual laboratories involved in the TOPMed consortium.

"This study is an important step towards developing precision medicine for at-risk and understudied minority populations," Burchard said, "But the current lack of genomic data from these populations highlights the urgent need for a dedicated national effort to prioritize diversity in research."

More information: Angel CY Mak et al. Whole Genome Sequencing of Pharmacogenetic Drug Response in Racially Diverse Children with Asthma, *American Journal of Respiratory and Critical Care Medicine* (2018). DOI: 10.1164/rccm.201712-2529OC

Provided by University of California, San Francisco